

Decision Memo for Cryosurgical Salvage Therapy for Recurrent Prostate Cancer (CAG-00064N)

Decision Summary

Revise the national noncoverage policy for cryosurgical salvage therapy to allow coverage only for those patients with localized disease who:

1. Have failed a trial of radiation therapy as their primary treatment, and
2. Meet one of the following conditions: Stage T2B or below, Gleason score < 9, PSA < 8 ng/mL.

Cryosurgical ablation as salvage therapy will continue to be noncovered for all other patients.

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Decision Memo

TO: Administrative File CAG-0064:
Cryosurgical Salvage Therapy for Recurrent Prostate Cancer

FROM:

Sean Tunis, MD, MSc
Director, Coverage and Analysis Group

John Whyte, MD, MPH
Acting Director, Division of Items and Devices

Samantha Richardson
Health Insurance Specialist

RE: National Coverage Decision

DATE: December 5, 2000

This memo serves four purposes: (1) outlines the description and treatment of prostate cancer, including primary and salvage therapies (2) reviews the history of Medicare’s coverage policies for cryosurgery ablation of the prostate, and provides a timeline of recent activities (3) presents and analyzes the relevant scientific and clinical data related to the use of cryosurgery as salvage therapy, and (4) delineates the reasoning in revising the national noncoverage policy and implementing a limited positive national coverage decision for patients wishing to choose this treatment as a salvage therapy after radiation.

Clinical Background

Prostate cancer is the most common cancer seen in men and is the second most common cause of cancer deaths in men. According to the American Cancer Society, adenocarcinoma of the prostate accounts for 47% of all new cancers detected in men, with an incidence of nearly 200,000 new cases per year. The number of cases is expected to increase dramatically over the next decade as a result of the aging of the population as well as improvements in, and access to, methods of diagnosis. Despite the high prevalence of this disease, the management of localized cancer remains controversial, with no standard clinical treatment algorithm. The two most common therapies are surgery (i.e., radical prostatectomy) and external beam radiotherapy. Within the past few years, brachytherapy and cryosurgery have gained attention as an alternative to surgery or radiation. Hormonal therapy is usually reserved for the symptomatic patient with systemic disease. Treatment and prognosis vary dependent upon the stage of cancer. See Table 1 for staging.

Table 1: Staging

Pathology	TNM
Digitally unrecognizable cancer	T1
<5% of TURP specimen, low to medium grade	T1A
>5% of TURP specimen, or high-grade tumor	T1B
Tumor detected by elevated PSA	T1C
Digitally palpable cancer, organ confined	T2
<½ of one lobe	T2A
>½ of one lobe	T2B
Cancer extending beyond prostate capsule	T3
Metastases	N or M
To lymph nodes	N1-N3
Distant	M1-2

Cryosurgery is a technique that induces cell lysis in the prostate by direct application of low temperatures. Although cryosurgery of the prostate was introduced in the early 1960's, inability to control the freezing process led to unacceptable complications and the procedure was quickly abandoned. The present technique as it relates to prostate cancer was developed in the early 1990's. More than 5000 procedures have been performed since 1991 when the Food and Drug Administration (FDA) granted a 510k clearance. The two main manufacturers are Endocare of Irvine, CA and Galil Medical of Woburn, MA.

Recurrent and residual disease after therapy are fairly common in prostate cancer, with rates ranging from 25% to 85%, depending upon initial therapy and disease type. The National Cancer Institute's CancerNet reports that about 10% of patients treated initially with radiation will relapse. Local recurrence presents a difficult challenge since there are limited therapeutic options. Additional radiation is rarely an option due to the limits on cumulative doses; hormonal therapy is not curative, and salvage prostatectomy has limited efficacy, with significant side effects. Survival estimates (five years) for salvage prostatectomy range from 25-65%. Salvage cryotherapy has been increasingly advocated as an additional therapeutic option.

FDA Review

These devices are pre-Amendment Class II devices. Because these devices are pre-Amendment, manufacturers of newer systems need only provide data that demonstrate substantial equivalence to a system that is already on the market. These substantial equivalence determinations have been based on functional performance, and have not required clinical data. That is, no human clinical trials were requested by, or submitted to FDA in order to obtain clearance for marketing.

History of Medicare's Coverage of Cryosurgery of the Prostate

In August 1993, the American Urological Association (AUA) published a position statement that cryosurgical ablation of the prostate (CSAP) is "investigational". This position made it increasingly difficult for providers and manufacturers to receive third party payment. There was no national policy by HCFA and thus there was significant carrier variation relating to coverage. HCFA first started to become involved in this topic in late 1994, when Cryomedical Sciences petitioned the agency to create a national coverage policy. In February 1995, HCFA informed Cryomedical Sciences that a national coverage policy could be established by either a randomized, prospective study being performed or the AUA changing their position statement. By spring, 1996, the AUA removed the experimental label from cryosurgery , stating: "cryosurgery is one of the methods of management of adenocarcinoma of the prostate. The long term curative efficacy of this treatment modality has not been established; when used, appropriate disclosure of facts of all other treatments should be made to the patient."

In August 1996 HCFA's Technical Advisory Committee (TAC) discussed the topic of cryosurgery of the prostate. The TAC consensus was that the evidence was insufficient to demonstrate the effectiveness and safety of cryosurgery for prostate cancer. Therefore, HCFA issued a national noncoverage decision. This noncoverage policy went into effect April 15, 1997. In addition, HCFA asked the National Cancer Institute and the AUA to consider co-sponsoring a multi-center study of this procedure. HCFA would agree to reimburse the medical service provided to Medicare beneficiaries within the study. HCFA also requested a technology assessment from the Agency for Health Care Policy and Research (AHCPR) to assess data concerning cryoablation as a salvage therapy, for those persons who failed radiation therapy. With the passage of the 1997 Balance Budget Act and the need for HCFA to focus on revamping its entire Medicare coverage process, the idea of a jointly-sponsored multi-center study was abandoned. Instead, in October, 1998 HCFA undertook a formal review of new data on cryosurgery. Based on this review, HCFA rescinded the national noncoverage policy on primary treatment and issued a new policy that allowed coverage for primary therapy. The noncoverage policy on salvage therapy remained in place. Since then, manufacturers and physicians have met with HCFA on multiple occasions to discuss new data.

Timeline of Recent Activities:

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| <i>June 15, 2000</i> | Representatives from Endocare met with members of the Coverage and Analysis Group at HCFA to informally discuss the coverage process and their options for pursuing coverage. |
| <i>July 5, 2000</i> | Endocare requested a formal review of the non-coverage policy for cryosurgery as salvage treatment for recurrent prostate cancer. |
| <i>August 28, 2000</i> | Galil Medical USA submitted a formal request for reconsideration of the national noncoverage policy. Since Galil provided additional information, the due date for a national determination was extended an additional 90 days. |
| <i>July-November, 2000</i> | HCFA supplemented the information provided by outside interested parties by independently conducting an extensive literature review. Search terms included combinations of "cryosurgery", "salvage" "prostate cancer", and "prostate adenocarcinoma". No new articles, other than those submitted, were found. |

Also received numerous comments from physicians and providers, who reported good outcomes.

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| <i>November 16, 2000</i> | American Urological Association submitted a position statement on salvage cryosurgical ablation of the prostate. |
| | Conference call with Galil Medical to discuss any outstanding issues concerning information they submitted. |
| <i>November 21, 2000</i> | |

Summary of Evidence

As noted earlier, AHCPR conducted a technology assessment in 1999, entitled "Cryosurgery for Recurrent Prostate Cancer Following Radiation Therapy". A total of seven studies from 1982-1998 were reviewed as part of the assessment. (Bales 1995, Cox 1995, Cespedes 1997, Miller 1996, Pisters 1997, Schmidt 1998, von Eschenbach 1995) All the studies consisted of uncontrolled case series of patients with cancer recurrence, who underwent approximately one-year followup. The assessment concluded that

"The available data suggest that some patients with radioresistant cancer have benefited from the use of cryosurgery as a salvage therapy. To date, studies indicate that at least in the short term, cryosurgery can result in negative post-treatment prostatic biopsies and low or undetectable serum PSA levels in some patients. Use of this technique has resulted in the biochemical disease-free survival of some patients. It may be reasonable to expect that some cancer-specific deaths of patients with radioresistant prostate cancer might be prevented or delayed by this procedure. Outcomes of salvage cryosurgery have tended to improve with improvements in instrumentation, technique, and experience; however, morbidity remains high and few patients have had long-term followup. Salvage cryosurgery prospective clinical trials are warranted and would help determine long-term survival benefits and make possible comparison of cryotherapy patient survival rates with those of untreated biopsy-positive patients."

Although this report was published in 1999, the latest study reviewed was 1998. Since then, six additional studies have been published, although two were published in abstract form. They are summarized below. All were retrospective case series (unclear if consecutive patients were studied), with a total of 620 patients. Note that no prospective trials were conducted. Specific information on each study can be found in **Appendix A: Literature Review**.

Pisters' (1999) objective was to identify a patient population that would benefit from the use of salvage cryosurgery. There were 145 patients involved in this study. All patients had locally recurrent adenocarcinoma of the prostate; 108 of these patients received previous radiation treatment. The authors found that those patients with a pre salvage cryotherapy of <10ng/mL and a history of radiation had an actuarial disease free survival rate at 2 years of 74%. Those patients who failed initial radiation therapy with a PSA > 10ng/mL and a Gleason score >9 were unlikely to be salvaged. The authors commented that their study had a short follow-up and had no way to distinguish those patients who were cured from those patients who may have received a delayed treatment failure. Due to the level of morbidity that is gained from this procedure, the authors recommended that the best recipients of salvage prostatectomy should be young and otherwise healthy. Pisters et al. stated that patients who have received prior hormonal and radiation therapy are less likely to benefit from aggressive salvage cryosurgery.

The Greene et al. (1998) article focused on the predictive value of the PSA nadir after salvage cryotherapy. The authors performed a study involving 146 patients who received salvage cryosurgical ablation. Of these 146 patients, 109 of them had received radiation prior to cryosurgery and 37 had received hormonal therapy prior to cryosurgery. After cryosurgery, 40% of the patients experienced decreased PSA levels. Greene found that the acceptable PSA nadir to indicate disease free survival was a PSA nadir of 0.5 ng/mL or less. Those patients with the lowest PSA nadir were found to have the best prognosis. Because their follow up period was relatively short, they felt that a longer follow up was needed to confirm the prognostic strength of salvage cryosurgery.

De la Taille et al. (2000) is the most recent study. He examined the records of 43 patients who underwent salvage cryosurgery from October, 1994 to April, 1999. All of the patients had biopsy proven recurrent prostate cancer after radiation therapy, and had received 3 months of combined hormonal therapy prior to receiving salvage cryotherapy. Biochemical recurrence free survival was 79% at 6 months and 66% at 12 months. In this study two different cryosurgical machines were used on the sample. The authors note that with the Food and Drug Administration's approval of a urethral warming device there has been a great advance in cryosurgical procedures. The authors believe that salvage cryotherapy is a viable option that can impact tumor control in biopsy proven local recurrence after radiation.

Perrotte et al (1999) completed and analyzed a survey that evaluated the quality of life after salvage cryotherapy. He surveyed 150 men who received salvage cryosurgery; the response rate was 74 percent. Patients commented on such complications as urinary incontinence, impotence, tissue sloughing, and problematic voiding and perineal pain. The overall satisfaction with salvage cryotherapy was 33 percent. The authors concluded that the quality of life for these patients may be compromised by the complications. The survey pointed to high levels of impotence in those patients who utilized the double freeze thaw cycle. Perrotte et al. felt that effective urethral warming cycles are essential to reduce the number of complications that arise after this therapy. He also comments that salvage cryotherapy when compared to salvage prostatectomy offers the same levels of morbidity and quality of life.

Lee et al (1999) looked at 56 patients with radiation therapy failure who underwent cryosurgery as salvage therapy from February, 1993- January, 1999. Patients were followed for a median of 12 months, with a range of 3-72 months. The authors separated patients into risk groups: low, moderate, and high. Disease Free Survival (DFS) was 56% for the low risk group, 44% for the moderate risk group, and 14% for the high risk group.

Chin et al (2000) presented an abstract at the Northeastern AUA section meeting in September, 2000. This study performed a predictive analysis of 118 patients with clinically localized biopsy-proven recurrent prostate cancer after radiotherapy. PSA and serial biopsies were conducted at 3,6,12, and 24 months. Follow-up ranged from 3 to 60 months. PSA follow-up showed 51.6%, 26.9% and 21.5% for levels <0.5, 0.5-5.0, and > 5.0 ug/L. 3.5% biopsy cores were positive. 22% were deemed clinical and/or biochemical failure. The authors concluded that criteria for favorable outcome included low stage and prostate volume, Gleason < 7, PSA < 8 and no prior TURP.

Unpublished data

In addition to the above articles, HCFA also received unpublished data from Drs. Jeffrey Cohen and Ralph Miller at Allegheny General Hospital. They presented five-year data for a total of 104 patients, 58 who underwent radiation only, and 46 who underwent androgen deprivation and radiation. Mean age was > 65 years. At five years, 20/53 patients had a PSA < 0.5 ng/ml.

Position Statements

In response to the posting on the website, the AUA submitted on November 16 a position statement on salvage cryosurgical ablation of the prostate. They reviewed six series of patients that have been published, summarizing efficacy and complications. They concluded that

"...there is inadequate data to establish the durable efficacy of cryosurgical ablation for local recurrence of prostate cancer after initial external beam radiation treatment in attempt to cure. In a situation that presents no consistently successful options, cryosurgical ablation of the prostate for patients who fail radiation therapy for carcinoma of the prostate is a treatment option. There is some evidence that there is a PSA response to treatment and many patients will have a negative biopsy but follow-up remains very short in published series. The relative contribution of neoadjuvant or adjuvant hormonal therapy given in many series is unknown. Thus, how CSAP would compare to just hormonal therapy alone is uncertain. Complications seem to occur to some extent in most patients with high rates of incontinence and impotence..."

Other Information

Nearly 20 people, primarily physicians and patients, have written to the agency describing their experience with salvage CSAP. All had good outcomes, and wanted to promote patient's access to this therapy.

Analysis/Issues Related to Coverage

In addressing the national noncoverage policy regarding cryosurgery as salvage therapy for the treatment of recurrent prostate cancer, the following questions arise:

- Is the evidence adequate to determine the effectiveness of cryosurgery as salvage therapy for recurrent prostate cancer?
- Is the evidence applicable to the Medicare population?
- Are the outcomes clinically and functionally relevant?
- Who is the appropriate population?

In order to address the **adequacy of the evidence**, several issues need to be discussed. These include study design, number of patients, length of followup, and complication rates.

Relating to study design, it is important to recognize that there is a hierarchy of evidence based on the methodology employed in a study. The most rigorous, well-designed studies, are prospective randomized clinical trials; however, such studies are not possible in every situation. In cancer research, well-designed trials are especially important given the morbidity and mortality of both the disease and treatment. Unfortunately, there are no prospective randomized clinical trials on salvage therapy. Given that, one must look closely at the case series, ensuring proper inclusion/exclusion criteria and appropriate statistical analysis to minimize bias.

In the studies presented, all had fairly well-established inclusion/exclusion criteria. Investigators ensured that patients had recurrent prostate cancer, and the type and grade were usually stated. However, the precise criteria varied across studies. Moreover, it is unclear how patients were selected, since the analyses were entirely retrospective. Such an analysis has selection bias, and makes it difficult to determine the true effect. When looking for reproducibility of results, it is important to be looking at similar populations. The data submitted does not allow those comparisons to be made across studies, nor does it allow us to accurately compare these results to alternative salvage therapies.

Although the therapeutic intervention was fairly standardized, the technique did change slightly over time. This likely improvement in technique could possibly skew the results, underestimating the true effect. Although there were no multicenter trials, the studies were conducted at different sites by different investigators. However, most surgeries were performed by one or two surgeons at these sites.

The AHCPR report expressed concern over the small number of patients enrolled (276 patients, and the short followup (average 12 months). The report also expressed some concerns about complication rates. Since the report was issued, an additional six studies have been submitted with a total of 620 patients. In addition, the followup time has doubled to 24 months, with a range of 0.3 to 72 months. Although longer follow-up is reported, there is limited statistical analysis provided. At times, actuarial data is submitted; at other times, only a range is reported. The imprecision of data points makes it difficult to determine the true DFS.

Table 2: Disease Free Survival and Length of Followup for the Various Studies

Authors and Year	Number of patients	Mean Age and Range of Patients	Disease Free survival (DFS) Rate	Length of Follow up	Adverse Events
De la Taille A, Hayek O, Benson MC, et al. 2000	43	69.4 years	79% DFS at 6 months	21.9 month mean follow up	Rectal pain 26%

Authors and Year	Number of patients	Mean Age and Range of Patients	Disease Free survival (DFS) Rate	Length of Follow up	Adverse Events
		(48.1-83.6)	66% at 12 months	(1.2-54 months)	Scrotal edema 12% Incontinence 9% Urinary Infection 9% Obstruction 5% Urethral stricture 5% Hematuria 5%
Perotte P, Litwin MS, McGuire , et al. 1999	112	63 years (45-81)	N/A	16.7 month mean follow up (0.5-31.5 months)	Incontinence 72% Sloughing 10% Impotence 59%

Authors and Year	Number of patients	Mean Age and Range of Patients	Disease Free survival (DFS) Rate	Length of Follow up	Adverse Events
					<p>Perineal pain 44%</p> <p>Bowel symptoms 24%</p>
Greene GF, Pisters LL, Scott S. 1998	146	Not reported	<p>40% DFS by PSA <0.5 ng/mL</p> <p>78% DFS by biopsy</p>	21 month follow up (3 –47 months)	Not reported
Pisters LL, Perrotte P, Scott SM, et al. 1999	145	Not reported	74% DFS at 24 months for pts with PSA < 10. 28% DFS at 24 months of PSA > 10. 58% DFS for Gleason score < 8, 29% DFS Gleason >9.	24 month follow up (3-48 months)	Not reported
Chin JL, Pautler S, et al 2000 (abstract)	118	Patients < 78 years	78% DFS	3-60 months	<p>Fistula 2.2%</p> <p>Severe incontinence 5.5%</p> <p>Bladder Outlet Obstruction 7.9%</p>
Lee F, Bahn DK, Badalament RA 1999 (abstract)	56	Not reported	2 year actuarial DFS:	12 months median followup	Incontinence 12%

Authors and Year	Number of patients	Mean Age and Range of Patients	Disease Free survival (DFS) Rate	Length of Follow up	Adverse Events
			56% for low risk group; 44% for moderate risk group; 14% for high risk group	Range of 3-72 months	Bladder Outlet Obstruction 9% Rectal Injury 12%

The discussion as to appropriate followup time provides an interesting debate. In general, five-year followup is the convention in oncology research. However, such outcome measures are more often for primary therapy and may not be as relevant for salvage therapy. Although salvage prostatectomy does typically report five-year data, hormonal therapy for patients with recurrent prostate cancer has limited five-year data. Moreover, there is considerable debate over the significance of a "hard and fast rule" of five-year data before a therapy can be considered effective in any patient population. Greene (1997) demonstrated that PSA nadir, typically reached at 3 months, was a good prognosticator of success. Investigators from Galil Medical have also asserted that PSA nadir or biopsy within the first few months from treatment, is a good predictor of success. As a result, multiple studies of five-year data may not be as necessary in this circumstance, as would be the case for most other cancer treatments.

In terms of **clinically and functionally relevant outcomes**, the authors do measure important outcomes, such as Disease Free Survival. Clearly, one needs to know whether this therapy works. At the same time, it is helpful to determine potential adverse events. Several authors have discussed the number of complications occurring with this therapy. These complications can be significant, with incontinence, rectal pain, impotence, and edema the major events. It is important to note that the technology appears to be improving over the past few years. There is improved instrumentation, specifically, temperature monitoring and urethral warming, as well as a variable number and positions of cryoprobes. These enhancements may potentially reduce the morbidity that is typically associated with this procedure. Moreover, all the available salvage therapies have associated morbidities. Patients undergoing cryotherapy have shorter hospital stays, typically 24 hours – 48 hours versus 7-9 days for patients undergoing salvage prostatectomy. In addition, cryosurgery patients do not usually require transfusions, as do many salvage prostatectomy patients.

Given that the results are applicable in the clinical/research setting, one must then ask whether these same results are **applicable to the Medicare population**. In general, prostate cancer is a disease of elderly men. Most of the studies enrolled a large number of Medicare beneficiaries, with a range on institutions. There were no complicated protocols, so it is unlikely that the results are not generalizable. However, there may be a technique-dependent complication rate; since most procedures were done by a small number of investigators, less-experienced physicians may have higher complications

Finally, one needs to consider the **appropriate patient population** in determining coverage. Several studies stratified data, based on stage of cancer. Moreover, investigators from Endocare presented data to HCFA, delineating outcome measures by stage. In general, such information is helpful in determining coverage policies. The issue as to appropriate patient population rests largely on the morphology of the disease; that is, does the disease change significantly by such factors as staging, age, co-morbidities, etc? Moreover, does the benefit of the therapy change for different patient groups? In this setting, the data for specific stages of malignancy are limited, although suggestive that patients with low to moderate risk gain the most benefit from this procedure. A careful review of the patients studied suggests that low to moderate risk can be defined as the presence of one or more of the following: PSA < 8 ng/mL, Gleason score <9, Stage T2B or below.

In conclusion, the data reviewed are primarily retrospective, case series, which are particularly prone to bias and which makes causality difficult to determine. We would have preferred to see longer follow-up, with fewer complications. At the same time, however, there is some evidence that some patients (within a narrow range of Gleason scores, PSA, and Stage) are likely to benefit from this procedure. Given that radioresistant, recurrent prostate cancer is a serious disease, with limited therapeutic options, cryosurgical ablation can be considered a reasonable and necessary procedure. In other words, cryosurgery is being covered as salvage therapy, with limited data since prostate cancer is a serious disease, and current alternatives are minimal. Moreover, the risks associated with salvage cryosurgery, although real and definable, are no greater than currently covered treatments. If more options become available to patients, or if more data becomes available, a different conclusion on reasonable and necessary may be warranted.

We would like to see prospective trials, or studies with more methodologic rigor. Despite prostate cancer being a common disease, there are few well-designed studies showing the effectiveness of various therapies, especially vis-à-vis each other. For recurrent prostate cancer, there currently exists no medical consensus regarding a standard approach. The two most common therapies, salvage prostatectomy and hormonal therapy, both have advantages and disadvantages. Patients with recurrent cancer need more treatment options, and more data needs to be collected on all these therapies.

Even though the information submitted as part of this decision is referred to as "studies", it is important to note that there were no true trials, which require a prospective design. Although not absolutely required for Medicare coverage in all situations, trials do provide critical information about treatment effect. We encourage physicians, patients, device manufacturers, and others to review the recent National Coverage Determination on Clinical Trials. This policy details the implementation of the President's Executive Memorandum on covering routine patient care costs for Medicare patients enrolled in clinical trials. Such provision of Medicare funding is designed to help the Medicare program answer questions about the effectiveness of therapies on Medicare patients. It would be particularly interesting to see a well-designed, prospective, randomized, trial comparing the different therapies (prostatectomy, hormonal therapy, and cryosurgery as well as new ones that are in early development) both for patients with primary and recurrent disease. Such information will dramatically help both physicians and patients make better-informed choices as to the appropriate therapy. We are interested in looking at all of these therapies within three years, as more information becomes available on all these therapies. Such information can help guide a more comprehensive coverage policy relating to treatment options for Medicare beneficiaries with prostate cancer. We encourage interested parties to meet with us to discuss possible study designs.

DECISION:

Revise the national noncoverage policy for cryosurgical salvage therapy to allow coverage only for those patients with localized disease who:

1. Have failed a trial of radiation therapy as their primary treatment, and
2. Meet one of the following conditions: Stage T2B or below, Gleason score < 9, PSA < 8 ng/mL.

Cryosurgical ablation as salvage therapy will continue to be noncovered for all other patients.

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